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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Nakayuki YAMAMOTO et al.

Serial No. 08/913,056 Appeal No. _____

Filed October 22, 1997 (GROUP 1617)

MUCOSAL PREPARATION CONTAINING PHYSIOLOGICALLY ACTIVE PEPTIDE

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS:

1. Real Party in Interest

The real parties in interest in this application are the assignees, Asahi Kasei Kogyo of Osaka, Japan, and Hisamitsu Seiyaku of Saga, Japan.

2. Related Appeals and Interferences

Appellants are unaware of any other appeal or interference which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. Status of Claims

Claims 1-27 are pending in this application, and the present appeal is taken from the final rejection of all of claims 1-27.

4. Status of Amendments

An Amendment after Final Rejection was filed May 11, 1999. There ensued an Advisory Action mailed June 4, 1999, which indicated that the Amendment after Final Rejection would

be entered upon filing an appeal. Therefore, the claims on appeal are as amended by that amendment, and as shown in the accompanying appendix.

5. Summary of Invention

The invention is a pharmaceutical composition that allows greatly improved transmucosal administration of physiologically active peptides. The compositions of the invention have three principal components, namely (a) a physiologically active peptide, such as insulin or calcitonin (the active ingredient), (b) an absorption promotor that promotes absorption of the physiologically active peptide by nasal or rectal mucosa, and (c) a compound that has vasodilating activity without causing mucosal irritation (see, e.g., page 1, lines 6-9 of the present specification).

Conventionally, physiologically active peptides such as insulin and calcitonin are administered by injection, which is disadvantageous in that injections are painful, and not all patients are able to self-administer an injection (see page 1 of the specification).

Oral administration of physiologically active peptides is also unsatisfactory, because the active ingredient is digested before it can be absorbed into the patient's blood stream (see page 1, lines 20-23).

Numerous attempts have been made to formulate a physiologically active peptide with an absorption promotor, to permit transmucosal administration with satisfactory uptake of the drug, and a number of such prior art efforts are chroni-

cled at pages 2-3 of the specification. However, none of the prior art formulations has been found to promote a satisfactory uptake of the active ingredient.

By contrast, the present inventors have discovered quite surprisingly that a three-component system as described above causes markedly increased absorption of the physiologically active peptide through the transmucosal administration route, by the combined use of an absorption promotor for transmucosal administration, together with a vasodilator that is a non-irritant on mucosal tissues.

The present invention therefore contributes an important new administration composition for physiologically active peptides, whereby the peptides can be administered in satisfactory yield through a less invasive route, and one which is easier for patients to tolerate and self-administer.

6. Issue

The sole issue on appeal is whether claims 1-27 would have been obvious, within the meaning of 35 USC §103, based on the collective teachings of the seven applied references, namely: MASIZ U.S Patent No. 5,645,854, ROBERTS et al. U.S. Patent No. 5,750,141, AZRIA et al. 5,149,537, KISSEL et al. ("Tolerability and Absorption Enhancement of Intranasally Administered Octreotide by Sodium Taurodihydrofusidate in Healthy Subjects", *Pharmaceutical Research*, Vol. 9, No. 1, 1992, pp. 52-57), Japan 3-5427, EPA-215697, and COOPER U.S. Patent No. 4,557,934.

7. Grouping of Claims

The claims are not grouped separately for purposes of the present appeal.

8. Argument

The primary reference to MASIZ is the only applied reference which discloses an active ingredient, a vasodilator and a permeation enhancer in combination; however, the delivery system of MASIZ is designed exclusively for transdermal administration, in contrast to the transmucosal formulation of the present invention, and the Examiner concedes that the primary reference fails to disclose or suggest the non-irritant vasodilators and transmucosal absorption promotors required by the present claims. For that purpose, the secondary references are relied upon, with ROBERTS et al. disclosing vasodilators including certain ones of those claimed, and with the remaining five secondary references being essentially cumulative of the prior art discussed at pages 2-3 of the present specification, in that they describe compositions for transmucosal administration comprising an active ingredient and an absorption promotor, but which lack the required vasodilator.

Therefore, the propriety of the rejection on appeal turns on whether, absent the teaching of the present invention, the skilled artisan would have had the requisite motivation to replace the irritant vasodilators of MASIZ with suitable vasodilators for transmucosal administration such as

those exemplified in ROBERTS, and further to replace the transdermal permeation enhancers of ROBERTS with any of the transmucosal absorption promotors of the remaining five secondary references.

However, a critical shortcoming of MASIZ for reference purposes relative to the claimed invention, is that the primary reference contemplates solely transdermal delivery of its active ingredient, and therefore not only fails to disclose or suggest the claimed vasodilators and absorption promotors suitable for transmucosal delivery, but also destroys any motivation to substitute components selected for use in one type of administration system, for use in an entirely different administration route.

Of course, consideration of whether a proper motivation existed for a proposed combination of references is central to reviewing the propriety of any obviousness rejection; therefore, the Examiner's rationale on this critical question would be of great interest. However, upon reading the text of the final rejection, we find that no rationale whatsoever has ever been offered for the rejection on appeal. Instead, we find only at the top of page 3 of the final rejection the conclusory allegation that "[i]t would have been obvious to use the claimed vasodilators in the Masiz et al. composition in view of Roberts et al. and to use the particular claimed absorption enhancers in view of [the remaining five secondary references]." Plainly, the statement of such a mere conclusion on the central issue in an obviousness

rejection, fails to discharge the Examiner's burden of making any *prima facie* case of obviousness. As such, the final rejection creates an unmistakable impression of an impermissible hindsight reconstruction of the claimed invention, and is fatally defective as a matter of law. Reversal of the rejection is therefore warranted.

The Examiner disputes that the primary reference contemplates solely transdermal delivery, but there is no disclosure anywhere in the patent that discusses any other route of administration. The Examiner points to claim 16, and in particular the mention of saliva, as an indication that transmucosal administration is "indicated".

However, a full consideration of the references confirms that such a conclusion is inaccurate. In particular, column 5, lines 19-34 reveal that the MASIZ composition is in the form of a complex held together by a water-soluble gum. Saliva is disclosed solely in the context of a laundry list of body fluids having non-neutral pH, which serve to dissolve the gum to release the active ingredient. Therefore, this disclosure confirms that transmucosal delivery is in no way contemplated. That is, the complex must stay together through the route of administration, and only upon arrival at the intended destination should it release the active ingredient.

Moreover, the mention of saliva would not in any event suggest transmucosal administration, because although the mouth contains mucosal tissue, transmucosal administration of pharmaceuticals is effected through the nasal or rectal

mucosal tissue. This is simply because, when a substance is placed in the mouth of a patient, the path of least resistance is ingestion, not transmucosal absorption. As described at page 1, lines 20-23 of the present specification, oral administration is unsuitable for the physiologically active peptides of the present invention.

The Examiner also argues that the vasodilator of MASIZ is not necessarily an irritant. Despite the "and/or" language in the abstract of the patent, however, all of the disclosed vasodilators of the reference <u>are</u> irritants, and a full reading of the reference indicates that the terms are used interchangeably. Indeed, the vasodilator of MASIZ is necessarily an irritant, to promote absorption of the active ingredients through the notoriously difficult transdermal route. Moreover, substances which are irritants on the skin will be all the more irritating to mucosal tissue, and unsuitable for use in the present invention.

In the Advisory Action of June 4, 1999, the Examiner at item 4 of Form PTOL-303 raises two further points in defense of the rejection on appeal: first, he contends that a vasodilator need not be a counter-irritant. That observation is correct, as is evidenced by the disclosure of the present specification. However, the more relevant point is that the vasodilators of the primary reference <u>are</u> exclusively irritants, contrary to that which is claimed, and furthermore <u>should</u> be irritants according to the teaching of the primary

reference. Thus, the more relevant considerations militate strongly against affirmance of the rejection on appeal.

The Examiner's second point in the Advisory Action is that the "ambient" saliva indicates delivery within the mouth. In response to this, appellant notes firstly that the term "ambient" used by the Examiner does not appear in the reference, and no basis for such an interpretation can be discerned. More fundamentally, as explained above, transmucosal administration does not occur orally in practice, such that the only stated connection between the teachings of the primary and secondary references simply does not exist.

9. Conclusion

From the foregoing discussion, therefore, it is believed to be apparent that the rejection of claims 1-27 based on the proposed combination of MASIZ in view of the six secondary references, cannot properly be affirmed but instead must be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

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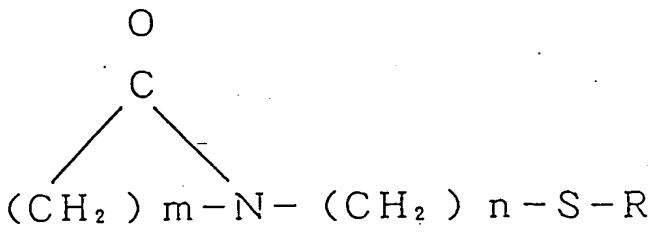
10. Appendix

The claims on appeal:

1. A preparation for transmucosal administration comprising (a) a physiologically active peptide admixed with (b) an absorption promotor having absorption promoting action for the physiologically active peptide on nasal mucosa or rectal mucosa, and (c) a compound having vasodilating activity without mucosal irritation.

2. The preparation for transmucosal administration according to claim 1 wherein the absorption promotor hvaing absorption promoting action for the physiologically active peptide on nasal mucosa or rectal mucosa has the absorption promoting action with impoved absorption rate of above 200% on nasal mucosa or rectal mucosa as compared with a preparation without absorption promotor when insulin is used as the physiologically active peptide.

3. The preparation for transmucosal administration according to claim 1 wherein the absorption promotor is a member selected from the group consisting of salt of bile acid, salt of fusidic acid, salt of glycyrrhizic acid, salt of O-acyl-L-carnitine, phospholipid, non-ionic surface active agent, cyclodextrin, higher fatty acid, 1-alkyl-2-pyrrolidone derivative, 1-dodecylazacycloheptane-2-one, bacitracin, sodium azulenesulfonate, azacycloalkane derivative of the formula[1]



(1)

wherein R is an alkyl, m is an integer of 2 - 4 and n is an integer of 1 - 15, provided that R is an alkyl with a carbon number of 5 - 11 in case where n is 1 - 3, and mixtures thereof.

4. The preparation for transmucosal administration according to claim 3 wherein salt of bile acid is a member selected from the group consisting of sodium taurocholate, sodium glycocholate, sodium deoxycholate, and mixtures thereof.

5. The preparation for transmucosal administration according to claim 3 wherein salt of fusidic acid is a member selected from the group consisting of sodium fusidic acid, tauro-24, 25-dihydrofusidic acid, and a mixture thereof.

6. The preparation for transmucosal administration according to claim 3 wherein salt of glycyrrhizic acid is a member selected from the group consisting of salt of glycyr-

rhizic acid, disodium 3-succinyloxyglycyrrhizic acid (carbenixolon), and a mixture thereof.

7. The preparation for transmucosal administration according to claim 3 wherein salt of O-acyl-L-carnitine is O-acyl-L-carnitine having C_{8-18} acyl.

8. The preparation for transmucosal administration according to claim 3 wherein salt of O-acyl-L-carnitine is a member selected from the group consisting of salt of O-octanoyl-L-carnitine, salt of O-lauroyl-L-carnitine, salt of O-palmitoyl-L-carnitine, and mixtures thereof.

9. The preparation for transmucosal administration according to claim 3 wherein phospholipid is a member selected from the group consisting of phosphatidylcholine (lecithin), lisophosphatidylcholine (lysolecithin), lysophosphatidylglycerol, and mixtures thereof.

10. The preparation for transmucosal administration according to claim 3 wherein non-ionic surface active agent is a member selected from the group consisting of polyoxyalkylene higher alcohol ether, polyoxyalkylene alkylphenol, sucrose fatty acid ester, and mixtures thereof.

11. The preparation for transmucosal administration according to claim 3 wherein non-ionic surface active agent is a member selected from the group consisting of polyoxyalkylene lauryl, polyoxyalkylene (24) cholesteryl ether, and a mixture thereof.

12. The preparation for transmucosal administration according to claim 3 wherein cyclodextrin is a member selected from the group consisting of α-cyclodextrin, ß-cyclodextrin, τ-cyclodextrin, dimethyl- ß-cyclodextrin, and mixtures thereof.

13. The preparation for transmucosal administration according to claim 3 wherein higher fatty acid is higher fatty acid of C_{16-20}.

14. The preparation for transmucosal administration according to claim 13 wherein higher fatty acid of C_{16-20} is a C_{18} higher fatty acid selected from the group consisting of oleic acid, linoleic acid, linolenic acid, and mixtures thereof.

15. The preparation for transmucosal administration according to claim 3 wherein 1-alkyl-2-pyrrolidone derivative is C_{4-12} alkyl.

16. The preparation for transmucosal administration according to claim 15 wherein alkyl is a member selected from the group consisting of butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and mixtures thereof.

17. The preparation for transmucosal administration according to claim 3 wherein azacycloalkane derivative of the formula (1) is azacycloalkane derivative in which R is C_{10} alkyl, m is 3 and n is 2.

18. The preparation for transmucosal administration according to claim 1 wherein the absorption promotor is admixed with 0.01 - 5 weight % of the said preparation.

19. The preparation for transmucosal administration according to claim 1 wherein the compound having vasodilating activity is a member selected from the group consisting of calcium channel blocker of molecular weight 200 - 700, prostaglandin E1, isosorbide dinitrate, nitroglycerin, and mixtures thereof.

20. The preparation for transmucosal administration according to claim 19 wherein calcium channel blocker is a member selected from the group consisting of diltiazem hydrocholoride, verapamil hydrochloride, bepridil hydrochloride, nifedipine hydrochloride, nicardipine hydrochloride, fasudil hydrochloride, and mixtures thereof.

21. The preparation for transmucosal administration according to claim 1 wherein the compound having vasodilating activity is admixed with below 1/2 of minimum usual dose as an effective component of the said compound in the preparation for transmucosal admininstration.

22. The preparation for transmucosal administration according to claim 1 wherein molecular weight of the physiologically active peptide is 300 - 10,000.

23. The preparation for transmucosal admininstration according to claim 1 wherein the physiologi-

cally active peptide is selected from the group consisting of insuline, calcitonin, human PTH (1 - 34), calcitonin gene related peptide (CGRP), angiotensin II, vasopressin, desmopressin acetate, buserelin acetate, goserelin acetate, nafarelin acetate, leuprorelin acetate, somatostatin, glucagon, oxytocin, secretin, LH - RH, ACTH, TRH, TSH, ANP, derivatives containing synthetic or semisynthetic compound thereof, and mixtures thereof.

24. The preparation for transmucosal administration according to claim 23 wherein calcitonin is a compound selected from the group consisting of eel calcitonin, salmon calcitonin, porcine carcitonin, human calcitonin, chicken calcitonin, and mixtures thereof.

25. The preparation for transmucosal administration according to claim 24 wherein eel calcitonin is ASU^{1-7} eel calcitonin (elcatonin).

26. The preparation for transmucosal administration according to claim 23 wherein insulin is a compound selected from the group consisting of human insulin, porcine insulin, bovine insulin, and mixtures thereof.

27. The preparation for transmucosal administration according to claim 1 wherein the preparation for transmucosal administration is a preparation for administration in nasal mucosa, oral mucosa, pulmonary mucosa, rectal mucosa, vaginal mucosa or ocular mucosa.